APCRI Journal
Volume 26, Issue 2- 2024, Pg. No. 5-9
Peer Reviewed & Open Access Journal

Research Article

Adverse Effects Following Intradermal Anti-Rabies Vaccination: An Observational Study at the Largest Government Hospital of Rajasthan

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DOI: https://doi.org/10.24321/0973.5038.202408

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How to cite this article:
Butt A I, Rathore M, Kumari N, Singh D, Patel H. Adverse Effects Following Intradermal Anti-Rabies Vaccination: An Observational Study at the Largest Government Hospital of Rajasthan. APCRI J. 2024; 26(2): 5-9.

Date of Submission: 2024-11-02
Date of Acceptance: 2024-12-15

A B S T R A C T

Introduction: Rabies is a Lyssavirus-caused progressive, acute and lethal encephalomyelitis present in over 150 countries. Using cell culture vaccines (CCV) for post-exposure immunization is an efficient and safe preventative measure. Although CCVs are the least reactogenic, studies have shown mild to severe side effects.

Objectives: To estimate the proportion of patients experiencing adverse effects after receiving intradermal anti-rabies vaccination and describe their clinico-social profile at the anti-rabies clinic, SMS Hospital, Jaipur

Methods: A hospital-based, descriptive, observational study was conducted among 392 animal bite patients at the anti-rabies clinic of SMS Hospital, Jaipur, Rajasthan from August 2023 to January 2024. All the patients of animal bites of Category II and III (not receiving rabies immunoglobulin) were included in the study. The collection of data was done using a pre-designed, pre-tested semi-structured questionnaire, administered by the interviewer.

Results: Out of 392 animal bite patients, 301 were male (76.8%) and 91 were female (23.2%); 27% of the total reported experiencing adverse effects. Pain at the injection site (8.2%) was the most commonly reported symptom, followed by tingling sensation (4.6%), headache (4%), redness (3.6%), fever (3%), itching (2.3%) and fatigue (1.3%). Most of the symptoms appeared within 4 to 12 hours post-vaccination and resolved without any medication. No severe adverse effects following vaccination were reported.

Conclusion: Some reactions were noted after administration of the vaccine by intradermal route but most were mild and self-limiting, thus the anti-rabies vaccine is a safe and effective tool against rabies and can be administered safely by intradermal route.

Keywords: Rabies, Post-Exposure Prophylaxis, Ant-Rabies Vaccines, Adverse Effect, Intradermal

Introduction

Rabies is a vaccine-preventable, progressive, acute, and lethal encephalomyelitis caused by neurotropic viruses from the Lyssavirus genus, part of the Rhabdoviridae family in the Mononegavirales order.[1]

Rabies is present in over 150 nations. According to the World Health Organization (WHO) estimates, India accounts for 36% of the global rabies deaths.[2] In India, about 130–210 rabies deaths are reported in hospitals every year, and 6–7 million animal bites are reported under the Integrated Disease Surveillance Program (IDSP).[3] Post-exposure vaccination can prevent rabies, with cell culture vaccines like human diploid cell vaccine (HDCV), purified chick embryo cell vaccine (PCECV), and purified vero cell rabies vaccine (PVRV) being safer and more effective than older nerve tissue vaccines.[4]

Vaccines can be administered intradermally or intramuscularly, and WHO recommends different regimens based on exposure and immunization status, such as Essen (days 0, 3, 7, 14, 28), 4 dose Zagreb (days 0, 7, and 21), and Updated Thai Red Cross ID (days 0, 3, 7, 28) schedules.[5]

Although cell culture vaccines (CCVs) are considered to be the least reactogenic, studies have shown the occurrence of mild to severe side effects. Some of the most frequently observed side effects are pain and redness at the injection site, nausea, headache, muscle aches, and dizziness, and in rare cases, severe allergic reactions may occur, which may require immediate medical attention.[6] Many studies have examined the safety profile of rabies vaccines, highlighting both common and rare side effects; a study by Madhusudana et al. in India evaluated the safety of the intradermal rabies vaccine and found that local reactions such as erythema and itching were common but generally mild and transient. Systemic reactions were less frequent and included mild fever and malaise.[7] Another study by Sudarshan et al. assessed the safety of PCECV in a large cohort of Indian patients. The study reported that over 90% of vaccine recipients experienced no significant adverse events.[8] Rabies is the only disease where prophylaxis can be initiated post-patient exposure, and the anti-rabies vaccine is an effective tool for prevention, but in order to maximize vaccine safety and public health results, it is crucial to comprehend their side effects and make sure that any possible hazards are understood and appropriately addressed.

Our study aims to estimate the proportion of animal bite cases that experienced adverse effects following intradermal anti-rabies vaccination at the anti-rabies clinic (ARC) of SMS Hospital, Jaipur.

Methodology

A hospital-based, descriptive, observational study was conducted at the ARC of Sawai Man Singh (SMS) Hospital, Jaipur from August 2023 to January 2024. This is the largest ARC in the state of Rajasthan with an annual caseload of more than 5000 patients. The wounds were categorized according to the WHO recommendations for post-exposure prophylaxis. 392 cases of Category II and III animal bite cases receiving intradermal anti-rabies vaccination and who did not require rabies immunoglobulin were included in the study on a first come first basis after applying eligibility criteria.

A sample size of 392 was calculated at a 95% confidence interval and 5% absolute allowable error to verify that 36.4% experiencing any form of adverse effect following vaccination and expected 10% loss to follow-up.[9] Children less than 5 years of age, patients on any medications like immunosuppressant drugs, and patients receiving Rabies Immunoglobulin (RIG) were excluded. Participants were informed about the purpose and process of this study and were included in the study only after obtaining written informed consent. A government-approved PVRV provided free of cost at the ARC was used with the regimen 2-2-2-0-2 (updated Thai Red Cross Schedule) i.e. 0.1 mL of reconstituted vaccine per ID (intradermal) site on bilateral deltoids on days 0, 3, 7 and 28.

Data was collected using a pre-designed, pre-tested semi-structured questionnaire administered by the interviewer. The questionnaire included details about the clinico-socio-demographic profile of the animal bite patients. The survey consisted of open-ended and closed-ended questions. Closed-ended questions covered the type of animal bite, bite location, symptoms after vaccination, symptom onset time, allergy history, recent hospitalizations, current medications, family history of allergies, alcohol intake, and pregnancy status for women. Open-ended questions sought specifics on the type of animal bite, additional symptoms post-vaccination, actions taken to relieve symptoms, pre-existing illnesses, and food consumed before vaccination.

A follow-up was done after each vaccine session with the participants via telephonic conversation and confirmation on the next visit was done until the completion of their regimen. After being coded and organized into a master sheet in Microsoft Office Excel, the data was subsequently transferred to SPSS (IBM SPSS Statistics version 25) for analysis. For data entered into the MS Excel worksheet, data validation checks were carried out on a regular basis. The outcomes were presented as tables and graphs and reported as percentages and proportions. The study was conducted after obtaining ethical approval from the Institutional Ethics Committee (Ref no: 853MC/EC/2023) of Sawai Man Singh Medical College, Jaipur.

ISSN: 0973-5038
DOI: https://doi.org/10.24321/0973.5038.202408

Results

The study included 392 animal bite patients who visited the ARC at Sawai Man Singh Medical Hospital. The clinico-social profile of the study participants is shown in Table 1.

Out of 392 animal bite patients, 301 were male (76.8%) and 91 were female (23.2%). The age of the patients ranged from 5 to 73 years with the majority (252, 64.3%) being in the age group of 19–59 years. Most of the bites were by stray animals (76.3%) followed by pet animals (23.7%), and the dog was the most common animal reported (83.2%). Though the majority (75.8%) of cases were literate, however, only 59% of them had done wound washing. Further, only 37% had washed their wounds with soap and water for 15 minutes. The most common site of the bite was the lower limb (72.7%) followed by the upper limb (15.3%).

About every third case (27%) reported at least one adverse reaction after initiation of ID vaccination however, they were mild and self-limiting, as shown in Table 2.

The most common adverse effect was pain at the injection site (8.2%,), followed by tingling sensation (4.6%), headache (4%), redness (3.6%), fever (3%), itching (2.3%), and fatigue (1.3%). Most of the symptoms appeared within 4 to 12 hours post-vaccination and resolved without any medication. No severe adverse events following vaccination were reported.

Table 1.Clinico-Social Profile of Animal Bite Patients at SMS Hospital, Jaipur

N = 392

Variables	Categories	n (%)
Gender	Male	301 (76.8)
	Female	91 (23.2)
Age (years)	5–18	87 (22.2)
	19–59	252 (64.3)
	≥ 60	53 (13.5)
Literacy status	Literate	297 (75.8)
	Illiterate	95 (24.2)
Category of bite	II	364 (92.9)
	III	28 (7.1)
Site of bite	Upper limb	60 (15.3)
	Lower limb	285 (72.7)
	Trunk	25 (6.4)
	Head & neck	7 (1.8)
	Multiple	15 (3.8)
Type of animal	Dog	326 (83.2)
	Cat	41 (10.5)
	Monkey	12 (3.1)
	Others	13 (3.2)
Alcohol intake	Yes	15 (3.8)
	No	377 (96.2)

Table 2.Adverse Reaction Following Intra-Dermal Anti-Rabies Vaccination**

N = 392

Symptom	Percentage	No. of Patients
No adverse reaction	73.0	286
Type of adverse reaction experienced		
Pain	8.2	32
Tingling	4.6	18
Headache	4.0	16
Redness	3.6	14
Fever	3.0	12
Itching	2.3	9
Fatigue	1.3	5
Adverse reaction required hospitalization	0.0	0

**Since multiple responses were allowed, some patients reported more than one adverse reaction.

Discussion

Our study shows that 27% of animal bite patients experienced mild adverse reactions following intradermal anti-rabies vaccination. No severe adverse events following vaccination were reported. The most commonly reported symptom was pain (8.2%), followed by tingling, headache, redness, fever, itching, and fatigue. All reported reactions were self-limiting, and none of the patients required hospitalization. The majority of adverse effects observed after receiving the rabies vaccination as documented in the literature were local events, including pain at the injection site, redness, swelling, and induration. In contrast to PCECV, local responses are more commonly observed after HDCV, as per the US Centers for Disease Control and Prevention.

Our findings corroborate with other studies. Madhusudana et al. in their study evaluated intradermal rabies vaccination (IDRV) in India and observed that local reactions such as erythema and itching were common but were mild and transient, with negligible systemic reactions, like mild fever and malaise.[7] Also, Sudarshan et al., in their study on the safety of PCECV, found that more than 90% of patients experienced no adverse events.[8] In their study, mild local and systemic reactions were noted, which were self-resolving. Shankaraiah et al., in their study conducted at municipal hospitals in Bangalore, India, reported that no adverse reactions were observed to anti-rabies vaccines.[10] Diallo et al., in their study titled "Human rabies post exposure prophylaxis at the Pasteur Institute of Dakar, Senegal: trends and risk factors", reported that adverse events were observed after the first two doses by 6%

ISSN: 0973-5038
DOI: https://doi.org/10.24321/0973.5038.202408

of the patients (42/678) and after the third dose, by 3% (16/493). Most of them were minor: headache (46.5%), fever (31%) and pain at the injection site (22%), and most of them (74%) occurred on the same day of the vaccine injection and up to 7 days.[11] Hardanahalli et al. conducted a study at a government referral hospital in India, where 515 animal bite cases received IDRV using the updated Thai Red Cross regimen and observed that 9.7% of participants experienced adverse drug events: erythema: 11 (2.1%), itching: 16 (3.1%), pain: 11 (2.1%), induration: 4 (0.8%), and fever: 8 (1.6%); all of these were resolved without complications.[12]

Our study differed from the previous studies in that we excluded patients requiring immunoglobulin so as to achieve uniformity and unbiased results focusing completely on an intradermal vaccination protocol (using the updated Thai Red Cross Schedule) and without combining it with intramuscular administration. Our study observed a higher proportion of adverse reactions (27%) compared to Diallo et al. (6%) and Hardanahalli et al. (9.7%), but the nature of the adverse events remained mild and self-limiting.[11,12] This observed difference can be due to vaccine formulations (PCECV vs PVRV), administration regimens (Essen vs. Thai Red Cross), and methods of adverse effect assessment as in our study, follow-up with the participants was done using telephonic conversations which ensured better reporting of any adverse effects experienced by the patients as compared to some studies which relied on self-reporting by the patients. Due to the high number of patients requiring post-exposure prophylaxis in India, understanding the safety of the anti-rabies vaccine is important.

Study Limitations

Our study provides valuable data on the safety of intradermal anti-rabies vaccination, but it has some limitations; the reliance on self-reported symptoms during follow-up may introduce response bias, particularly for mild adverse reactions that might be underreported.

Conclusion

Our study confirms that although a few adverse reactions were observed in the patients after receiving intradermal anti-rabies vaccination, they were mild and self-limiting. Thus, we can conclude that intradermal rabies vaccination is a safe and effective tool for prevention of rabies. Rabies prophylaxis must not be interrupted or stopped, as incomplete vaccination can be fatal. Minor adverse events does not contradict future doses, but continuous scrutiny of vaccine safety and efficacy is crucial; any reaction, be it mild or severe, should be duly noted and addressed.

Conflict of Interest: None

Sources of Funding: None

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process: None

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ISSN: 0973-5038
DOI: https://doi.org/10.24321/0973.5038.202408